REMARKS

Claims 1 to 5, 7 to 11, 13 to 17 and 19 to 37 are now pending in the application, claims 6, 12 and 18 having been canceled and new claims 19 to 37 added by the above amendment. Applicants have amended claims 1 and 3 to recite that the 70 amino acids are contiguous and that the polypeptides reduce hepadnavirus replication. Support for these amendments can be found throughout the specification, e.g., at page 8, lines 21 to page 9, line 8. Claims 1and 3 have also been amended to recite that the nucleic acid sequences are operably linked to any of a variety of promoters. Support for these amendments can be found in the specification, e.g., at page 25, line 26, to page 26, line 12.

Support for new claims 19 to 22 can be found, e.g., at page 25, line 26, to page 26, line 12, page 3, lines 8 to 13, and at page 5, lines 8 to 10. Support for new claims 23 to 37 can be found, e.g., at page 3, lines 8 to 15, page 5, lines 8 to 10 and 19 to 21 and at page 25, line 26, to page 26, line 12. For example, the specification at page 5, lines 19 to 21 recites that the carboxyterminal amino acid of the first amino acid sequence can be any of the amino acids between position 71 and position 180, supporting claims that recite a specific core sequence(s) having a carboxyterminal amino acid within that range. The amendments and new claims add no new matter to the present application.

I. The Invention

The invention is based on applicants' discovery that altering the carboxyterminus of a hepadnavirus core protein creates a mutant polypeptide capable of reducing replication of a wild type hepadnavirus by a dominant negative mechanism. The inhibitory effect can be achieved using a core protein having a deletion of a few carboxyterminal amino acids. Such a mutant core protein can optionally be joined to a second protein. Nucleic acids encoding such polypeptides, as well as vectors and host cells containing the nucleic acids, are claimed in the present application.

II. Rejection under 35 U.S.C. § 112, first paragraph

Claims 1 to 18 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Specifically, the Office Action states (at page 2):

> [T]he specification, while being enabling for nucleic acids encoding polypeptides as shown in Figure. 1 and which reduce replication of a hepadnavirus in vitro, does not reasonably provide enablement for all nucleic acids encoding polypeptides having any 70 amino acids of wild type hepadnavirus core protein which do not have this activity.

Applicants believe that the claims are fully enabled as filed. However, in the interest of moving the claims toward allowance, applicants have amended claims 1 and 3 to recite that the 70 amino acids are "contiguous" and that the encoded polypeptide "reduces hepadnavirus activity." Claims 6, 12 and 18 have been canceled for reasons unrelated to the present rejection, thus obviating the rejection with respect to those claims.

As amended, claims 1 and 3 include functional limitations. Applicants believe these amendments address the Examiner's concerns about functional limitations, which were raised in the Office Action at page 3, lines 6 to 7. Amended claims 1 and 3 also require that the recited 70 amino acids be "contiguous." Applicants believe these amendments address the Examiner's concerns about the scope claims, which were raised in the Office Action at page 3, lines 14 to 20. Accordingly, applicants submit that amended claims 1 and 3 (and dependent claims 2, 4, 5, 7 to 11, and 13 to 17) are fully enabled and respectfully request that the present rejection be reconsidered and withdrawn. Applicants point out that new independent claims 23, 26 and 32 include language similar to that of amended claims 1 and 3 and submit that these new claims are fully enabled as well.

III. Rejection under 35 U.S.C. § 102

Claims 1, 2, 7, 8, 13, and 14 were rejected as allegedly anticipated by Beames et al. (Virology 194:597-607 (1993)). Beames is a publication that describes experiments involving introducing certain deletion mutations into the hepatitis B virus core protein, in order to

determine the effect of such mutations on capsid formation, encapsidation, reverse transcription and DNA synthesis (see, e.g., the abstract of Beames).

In the interest of moving the present application toward allowance, applicants have amended claim 1 to recite that the nucleic acid sequence is operably linked to one of a variety of promoters, i.e., promoters useful for initiating transcription in a target cell, such as a hepatocyte. Such an amendment is supported in the specification at page 25, line 26 to page 26, line 12.

Applicants submit that Beames does not describe nucleic acids that encode mutant hepadnaviral core proteins operably linked to one of the promoters recited in amended claim 1. Thus, applicants submit that Beames does not anticipate amended claim 1 (or claims 2, 7, 8, 13, or 14, which depend from claim 1) because Beames does not describe all of the limitations recited in this claim. Accordingly, applicants respectfully request that the present rejection be reconsidered and withdrawn.

Further, applicants have added new claims 23 to 25, which applicants submit are not anticipated by Beames for the reasons stated above. New independent claim 26 has also been added, which recites a nucleic acid that encodes a polypeptide consisting of an amino acid sequence identical to specific fragments of SEQ ID NO:12. Applicants point out that certain of Beames' polypeptides include linker encoded amino acids (see, e.g., Beames' Cd112, Cd148, Cd163, and Cd176, e.g., at Fig. 1A). Applicants respectfully submit that Beames does not disclose the specific fragments recited in claim 26 and that it does not anticipate that claim (or claims 27 to 31, which depend therefrom).

Claims 6, 12, and 18 were rejected as allegedly anticipated by each of Souw et al. (WO 94/12617) and Rutter (U.S. Patent No. 4,859,465). Applicants have canceled claims 6, 12, and 18, thus obviating these rejections.

IV. Rejection under 35 U.S.C. § 103

Claims 3 to 5, 9 to 11 and 15 to 17 were rejected as allegedly obvious over Souw in view of Beams. Specifically, the Office Action states (at page 7):

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the nucleic acid disclosed by Souw et al. to include

as the core protein element, the deletion mutants disclosed by Beams et al. having deletions of at least the carboxyterminal three amino acids, in the disclosed fusion protein, and to further include the nucleic acid in a vector, and in a cultured cell, since Souw et al. disclose that any hepadnavirus (e.g., HBV) core protein variant, including fragments thereof, in the disclosed fusion proteins.

One would have been motivated to include carboxyterminal deletions of the HBV core protein in the fusion proteins disclosed by Beams by the desire to express HBV antigens for the prevention or treatment of hepatitis or other undesirable consequences of HBV infection. The general teaching of any fragment or deletion of HBV core protein fused to a HBV surface protein is disclosed in the Souw et al. reference, and therefore was well known in the art.

As indicated above, applicants have amended claim 3 to recite that the nucleic acid sequences are operably linked to one of a variety of promoters. Applicants respectfully traverse this rejection in view of the amendment to claim 3 and for the reasons discussed below.

Souw is a publication that describes recombinant vaccinia viruses capable of expressing certain HBV epitopes, e.g., fusion proteins such as:

preS1-coreΔ8 (pre-S1 polypeptide fused to HBV core polypeptide having an 8 amino acid internal deletion; see Souw at page 63, lines 10 to 14),

preS1-complete core,

core-preS1* (which includes amino acids 1 to 145 of core, a 3 amino acid spacer, amino acids 1 to 56 of preS1, and a 4 amino acid tail; see Souw at page 73, lines 16 to 21),

core-preS2 (which includes amino acids 1 to 144 of core, a 1 amino acid spacer, amino acids 1 to 55 of preS2, amino acids 1 to 8 of S and a 4 amino acid tail; see Souw at page 74, lines 20 to 26), and

core-S* (which includes amino acids 1 to 144 of core, a 1 amino acid spacer, amino acids 107 to 163 of S antigen, and a 7 amino acid tail; see Souw at page 75, lines 16 to 25).

Souw discloses that plasmids encoding the described proteins should be configured so that the HBV sequences are under the control of a promoter active in vaccinia virus (see, e.g., Souw at page 34, lines 3 to 24). Souw does not appear to disclose, or suggest, nucleic acids that encode a polypeptide as recited in amended claim 3 linked to one of the recited promoters.

The Office Action cites a secondary reference (Beames) that does not provide the information missing in Souw, the primary reference. Beames is a publication that describes experiments involving mutating the hepatitis B virus core to determine the effect of such mutations on capsid formation, encapsidation, reverse transcription and DNA synthesis. Beames indicates (at page 598, col. 1 and 2) that Beames' deleted core genes were inserted into vectors containing the human metallothionein IIA promoter and into baculovirus transfer vectors. Beames discloses none of the promoters recited in claim 3. Beames does not disclose, or even suggest, the nucleic acids recited in claim 3, i.e., nucleic acids encoding core/surface protein fusion proteins linked to one of the promoters recited in claim 3. Nor does Beames (who was interested in studying the biology of HBV core protein by making a series of deletion mutants) provide any motivation to use other promoters.

Souw and Beames do not teach, or suggest, all of the limitations recited in claim 3. Thus, applicants respectfully submit that Souw and Beams cannot render amended claim 3 (or claims 4, 5, 9 to 11, 15 to 17, 21 and 22, which depend from claim 3) obvious, singly or in combination.

Further, applicants respectfully submit that a person skilled in the art would not have been motivated by these publications to modify nucleic acid sequences described in Souw with those described in Beames. Souw was solely interested in producing antigenic proteins that would raise an immune response against HBV. Beames did not disclose that any of Beames' HBV core protein deletion mutants would be useful for this purpose. Beames was not at all interested in raising an immune response – rather, Beames was focused solely on understanding the biological function of various parts of the core protein. Furthermore, some of Beames' deletion mutants contained additional, non-HBV residues at the carboxyterminus. Applicants respectfully point out that the Examiner has not explained why it would have been obvious to use those mutants in Souw's fusion proteins. Applicants submit that the disclosures of Beames are irrelevant to Souw's purpose, and would certainly not have been followed by one of ordinary skill seeking to find HBV core antigen epitopes for use in the vaccines of Souw.

For the reasons discussed above, applicants respectfully submit that claims 3 to 5, 9 to 11 and 15 to 17 are not rendered obvious over Souw and Beames and request that the present rejection be reconsidered and withdrawn.

Further, applicants have added new claims 32 to 37, which recite a nucleic acid encoding a fusion protein consisting of an amino acid sequence identical to specific fragments of SEQ ID NO:12 and an amino acid sequence identical to a portion of a wild type hepadnavirus surface protein. Applicants respectfully submit that neither Souw nor Beams, singly or in combination, teach or suggest these specific nucleic acids. Thus, applicants submit that claims 32 to 37 are not obvious in view of these publications.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Enclosed is a check for $475 for the Petition for Extension of Time fee for a three month extension and a check for $212 for the excess claims fee. Please apply any other charges or any credits to Deposit Account No. 06-1050, referencing Attorney Docket Number 00786-282003.

Respectfully submitted,

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